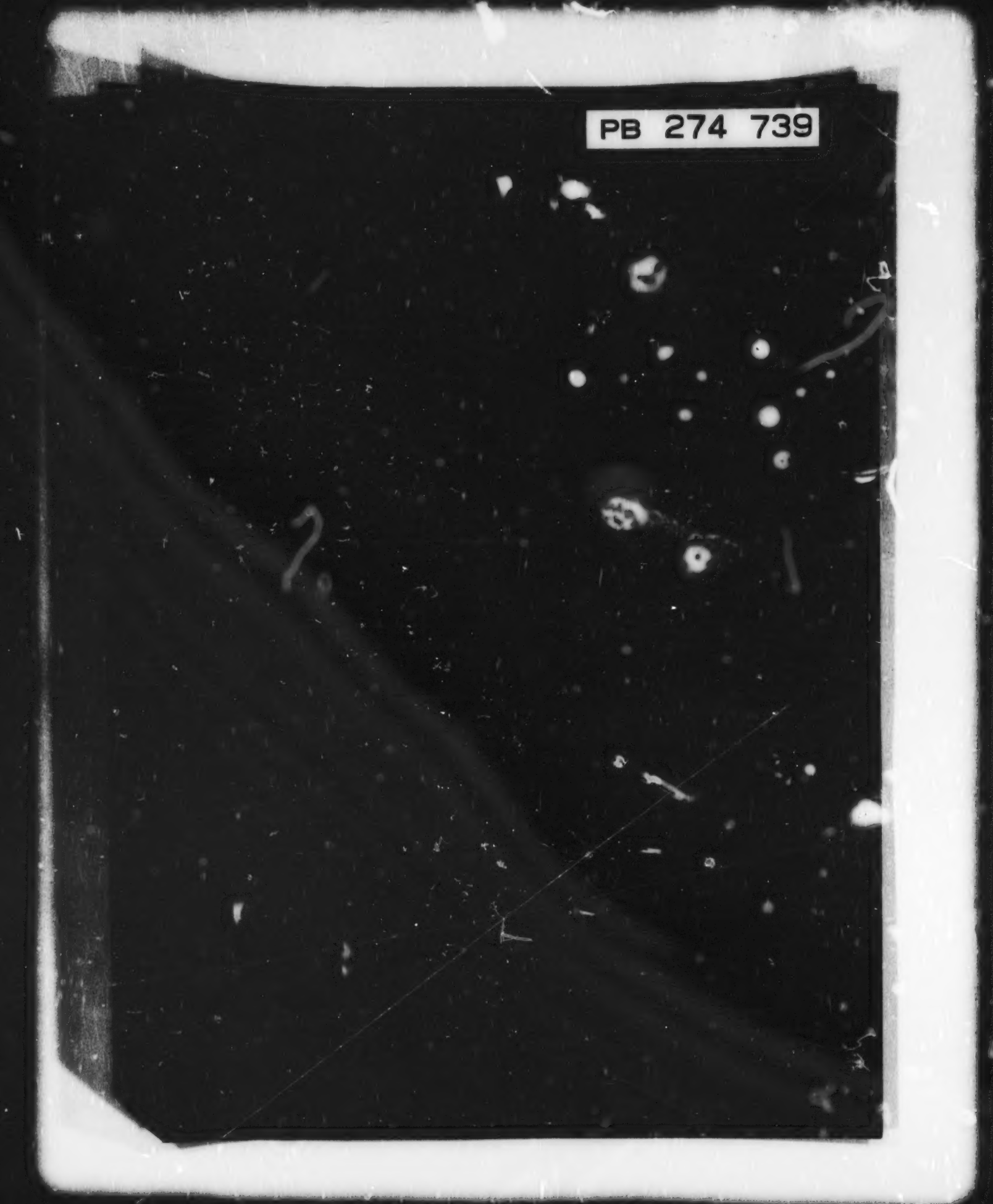
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On the Chemistry of the Isomeric Dichlorodiphenylacetaldehydes Related to DDT. Stereoelectronic Effects in the Hydrolysis of their Cyclic Acetals

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Received July 7, 1970[2]

The chemistry of the isomeric dichlorodiphenylacetaldehydes related to DDT was investigated to aid in delineating their possible role in the metabolism of this pesticide. In the case of the *p,p'*-isomer, the most important system under consideration, several literature syntheses were shown to be incorrect. The failure of at least one of these methods was attributed to the preferred oxidative involvement of the benzhydryl carbon via rearrangement of a β-hydroxy enol ether which normally led to the isolation of the *p,p'*-dichlorobenzophenone instead of the desired aldehyde. The *o,p'*-isomer exhibited chemistry similar to that of the *p,p'*-isomer although the steric effect of the ortho-substituted chlorine on the benzhydryl proton was notable. The *o,o'*-isomer was normal in that it did not undergo reactions involving the benzhydryl carbon. Some possible mechanistic and biological implications of the work are discussed.

La chimie des dichlorodiphénylacétaldéhydes isomères, apparentés au DDT, a été étudiée afin de délimiter leurs rôles possibles dans le métabolisme de ce pesticide. Dans le cas de l'isomère-*p,p'*, le système considéré comme le plus important, plusieurs synthèses données dans la littérature sont incorrectes. L'échec d'au moins une de ces méthodes est attribuée à l'entrée en jeu de l'oxydation préférentielle du carbone benzhydryle via une transposition d'un éther énolique β-hydroxylé qui normalement conduit au *p,p'*-dichlorobenzophénone au lieu de conduire à l'aldéhyde désiré. L'isomère-*o,p'* montre un comportement analogue à celui de l'isomère-*p,p'*, bien que l'effet stérique des substituants ortho sur le proton benzhydryle soit notable. L'isomère-*o,o'* a un comportement normal en ce sen qu'il ne subit aucune réaction impliquant le carbone benzhydryle. Certains mécanismes possibles et certaines implications biologiques de ce travail sont discutés.

Canadian Journal of Chemistry, 49, 3877 (1971)

Today DDT is of immense biological importance, with vast quantities now distributed in the worldwide environment. However, surprisingly little work has been done toward gaining a firm theoretical understanding of its chemistry. The synthesis of the isomeric dichlorodiphenylacetaldehydes related to DDT and a study of some of their reactions were undertaken to help correct this deficiency. Investigation of their role in DDT metabolism (1) seemed essential since they are the logical intermediates in the formation of the dichlorodiphenylacetic acids which are major metabolites. Although several syntheses have been reported for these aldehydes, our attempts to reproduce some of them led to contradictory results which are theoretically interesting and may be of biological consequence.

The several syntheses reported for *bis*(*p*-chlorophenyl)acetaldehyde (**1***a*) include the rearrangement of 1,2-*bis*(*p*-chlorophenyl)ethylene glycol (**2***a*) in a sealed tube under vigorous conditions to effect a phenyl migration (2) (eq. 1); the hydrolysis of the cyclic acetal (3), 2-(*p,p'*-dichlorobenzhydryl)-1,3-dioxolane (**3***a*) (eq. 2); the reductive cleavage of the pyrazolene **4***a* (4) (eq. 3). In all three cases the aldehyde was reported as a crystalline compound varying in m.p. from 135 to 149 °C.

The synthesis of **1***a* by the hydrolysis of **3***a* appeared straightforward and was especially attractive since the starting material for synthesis of **3***a* was 2,2-dichloro-1,1-*bis*(*p*-chlorophenyl)-ethane (DDD) which is readily available. Our attempts (5) to reproduce this method afforded crystalline **3***a* whose structure confirmation conveniently eliminated structures **5***a* and **6** which are conceivable products of this reaction proposed by Riemschneider and co-workers. However, the results of our hydrolyses of **3***a* confirm that the previous workers (3) had isolated 4,4'-dichlorobenzophenone (**7**) instead of the desired aldehyde (**1***a*). The aldehyde was obtained as an oil which could not be crystallized. The crystalline material isolated by the previous workers (2–4) is characteristic of **7** in varying degrees of purity. It was later found that other workers (6) had arrived at the same conclusion since their

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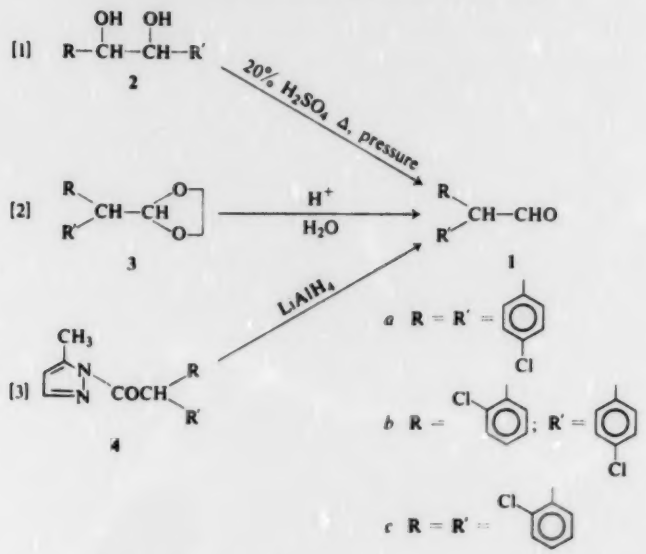
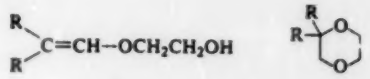
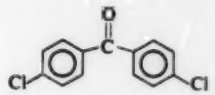
[2]Revision received August 31, 1971.



Darzens synthesis of the aldehyde had afforded an oily product. Investigation of this chemistry was undertaken since the chemistry encompassing the formation of the dichlorobenzophenone might have a bearing on its occurrence in DDT metabolism.



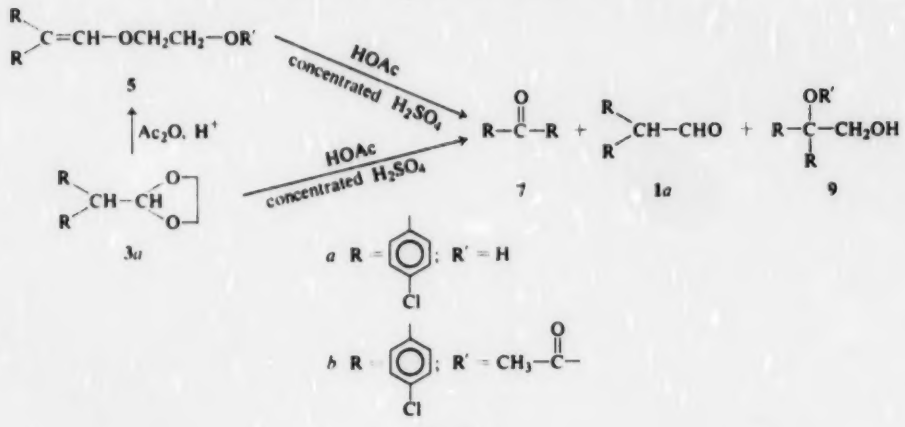


Based on these findings, it seemed plausible but mechanistically obscure that **1***a* might be intermediate in the formation of **7** during the hydrolysis of the acetal **3***a* under the heterogeneous conditions. However, the aldehyde was recovered in good yield when it was subjected to the conditions of hydrolysis with no appreciable conversion to dichlorobenzophenone (**7**). When the hydrolysis was carried out using mixtures of *p*-dioxane and 20% aqueous HCl (1:1 v/v), **7** was formed as the major characterizable product (30–60% yields) in 3–5 h at reflux temperature. There was no t.l.c. evidence for the intermediate formation of **1***a*. This result was supported by following the hydrolysis of **3***a* by n.m.r. under similar conditions.[3] Since the purity and structure of **3***a* have been rigorously established, an alternative route by which dichlorobenzophenone **7** can be formed from acid hydrolysis of acetal **3***a* without invoking the intermediacy of aldehyde **1***a* apparently exists. The experiments outlined in Scheme 1 were carried out with the objective of trapping or stablizing intermediates which might be responsible for the formation of **7** from acetal **3***a*.

Solvolysis of **3***a* in acetic acid in the presence of concentrated sulfuric acid at 100 °C for 1 h gave a mixture of the dichlorobenzophenone **7**, aldehyde **1***a*, and the acetoxyethanol **9***b*. These products were isolated by preparative t.l.c.[4] and

[3]The hydrolysis was carried out at 75° in *p*-dioxane-d_8 with 20% DCl. The n.m.r. scans were made at 5-min intervals for 1 h. The acetal apparently underwent immediate hydrolysis; however, there were no resonances indicating the formation of **1***a*. A control experiment had indicated that **1***a* was stable under these conditions.

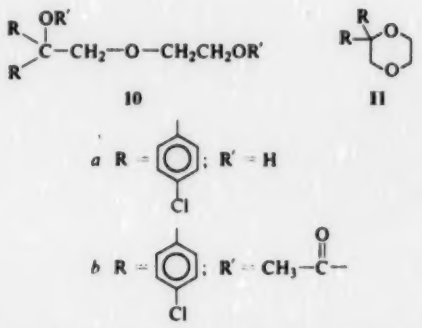
[4]The acetoxyethanol **9***b* decomposed on t.l.c. to two materials; one remaining at the origin and the other near the solvent front. The latter material characteristically fluoresced light blue under short wave u.v. light. The exact nature of these products will be discussed later; however, n.m.r. studies of product mixtures of **9***b* in the presence of the n.m.r. shift reagent (**7**), $Eu(DPM)_3$, confirmed that the acetate group (three proton, singlet) was associated with the benzhydryl carbon and a hydroxyl group was associated with the methylene group (two proton, singlet) since the latter group experienced the largest paramagnetic shift with the reagent while the aromatic signals experienced relatively little shift.



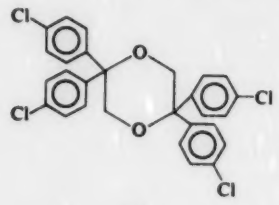
SCHEME 1

identified by their spectral properties. The benzophenone **7** constituted about 10–15% of the total along with major amounts of the aldehyde and acetoxyethanol. Solvolysis of the enol ether acetate **5***b*, which was obtained from **3***a* in good yield by treatment with acetic anhydride containing concentrated sulfuric acid, gave qualitatively but not quantitatively the same product mixture; the benzophenone **7** was formed in about 40% yield with appreciable amounts of the acetoxyethanol **9***b* and trace amounts of aldehyde **1***a*. It was also shown that neither **1***a* nor **9***b* were intermediate in the formation of **7** under the solvolysis conditions.

Since the enol acetate **5***b* affords **7** as a major product and the acetoxyethanol **9***b* is not intermediate in this conversion, the benzophenone **7** must have resulted from rearrangement of **5***b* itself or from some other yet undetected intermediate. Protonation of the enol ether acetate at the ether oxygen should activate the molecule to attack by acetate ion at the benzhydryl carbon or intramolecular attack by its own acetate group via a *quasi*-six-membered ring. The former possibility should have resulted in the diacetate **10***b*. However, this compound was not found among the products and suggested that **10***b*, if formed, possibly undergoes further cleavage at the ether oxygen to form the acetoxyethanol **9***b*, a major product of the acetic acid solvolysis reaction. Nevertheless, 2,2-*bis*-(*p*-chlorophenyl)-diethylene glycol (**10***a*) was synthesized according to the reported method (8), and its hydrolysis properties were investigated. The diethylene glycol could dehydrate in a cyclic fashion (9) to



form dichlorobenzophenone **7** or dehydrate to 2,2-*bis*(*p*-chlorophenyl)-*p*-dioxane (**11**) which could possibly undergo pyrolysis to **7**. Hydrolysis experiments with **10***a* repeatedly gave mixtures as determined by t.l.c. and gas chromatography (g.c.). The mixtures consisted primarily of two materials whose chromatographic properties were reminiscent of the decomposition products[4] of the acetoxyethanol **9***b*; one material was highly polar and polymeric in nature while the other material was relatively non-polar and fluoresced light blue under u.v. light. The latter material was purified by preparative t.l.c. and identified as the symmetrical *p*-dioxane **12**. The n.m.r. spectrum of **12** revealed the non-equivalency of the methylene protons, and Drieding models show that because of the steric requirements of the bulky phenyl groups the molecule prefers a twist-boat conformation in which the methylene protons experience different environments. The mass spectrum of the compound contained a parent ion greater than 500 (*m/e*)



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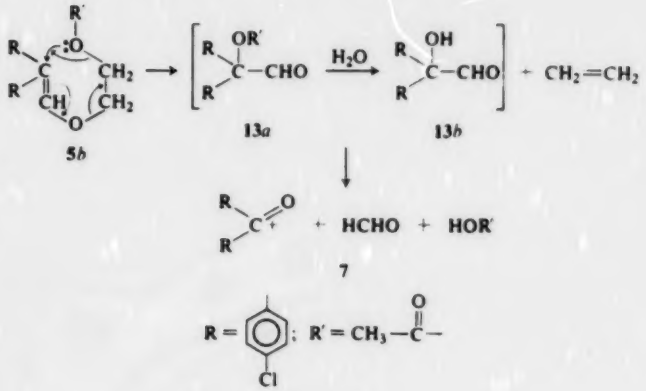
and was otherwise indicative of structure **12**. The dioxane **12** and polymeric products were also shown to be spontaneous decomposition products of the diethylene glycol **10***a* with or without solvent. The most plausible explanation for formation of such products would be that intramolecular hydrogen bonding may facilitate decomposition of the diethylene glycol **10***a* to the ethylene glycol **9***a* which in turn can undergo dimerization to **12** or polymerization. The dichlorobenzophenone **7** was only a minor decomposition product (<10%) of **10***a* and was detected by electron capture g.c. A small amount of dioxane **11** was also detectable among the products. Therefore, the intermediacy of **10***b* in the solvolysis of the enol ether acetate **5***b* seems likely since it would explain the presence of the acetoxyethanol **9***b* and polymeric material among the products. The formation of dichlorobenzophenone **7** from rearrangement of **5***b* is now credible and is shown in Scheme 2.[5] Invoking the intermediacy of an α-hydroxy aldehyde (**13***b*) in the formation of the dichlorobenzophenone **7** was attractive since such an intermediate would be expected to be both chemically and thermally labile and is a conceivable product in the other erroneous syntheses reported for aldehyde **1***a* by other workers. Although there is no chemical evidence to support the intermediacy of **13***a*, gas chromatography – mass spectrometry (g.c.–m.s.) confirmed its presence among the decomposition products of the enol ether acetate **5***b*. Gas chromatography on a 3% diethylene glycol succinate/2% orthophosphoric acid column at 170 °C gave eight peaks for pure enol ether acetate **5***b*, six of which were identified by their mass spectra. The first peak was the expected dichlorobenzophenone **7** in comparatively good yield having a base peak of *m/e* 139 $(R—C\equiv O)^+$ in its mass spectrum. The second peak was identified as the α-hydroxy aldehyde (**13***b*) whose mass spectrum also has a base peak of *m/e* 139 along with M (*m/e* 281), M-1 and M-HCHO (*m/e* 251) of intensities approximately 0.3% that of the base peak. The third peak was the expected aldehyde **1***a* in less than 10% yield of that of the ketone **7**. The fourth peak was a major component and was identified as the α-acetoxy aldehyde (**13***a*) although the parent molecular ion (*m/e* 313) was not discernible. However, there are prominent fragments corresponding to the loss of both HCHO (*m/e* 293) and HOAc (*m/e* 264) as well as the base peak of *m/e* 139. The presence of these fragments in the spectrum implies that both the aldehyde and acetate moieties must have been present in the original molecule. The detection of the parent ion of the α-hydroxy aldehyde (**13***b*) is probably a reflection of increased stability of this ion via hydrogen bonding. Both peaks five and seven were too weak to identify conclusively. Peaks six and eight were identified as the enol ether alcohol (**5***a*) and the enol ether acetate (**5***b*) respectively. The acidic column conditions favored decomposition since g.c. on a 3% SE-30 column at 212 °C gave smaller relative amounts of the major decomposition products. In fact, the α-acetoxy aldehyde (**13***a*) was not detectable under these conditions; however, this may also be a reflection of the poorer stability of acetate **13***a* under these conditions since the α-hydroxy aldehyde was detected. In addition, the introduction of the enol ether acetate **5***b* into the mass spectrometer by the direct probe inlet produced spectra indicating that extensive rearrangement had occurred.

In light of these data, it was suspected that similar intermediates could occur in the hydrolysis of **3***a* under aqueous acidic conditions affording dichlorobenzophenone **7**. Hydrolysis of the substituted dioxane **12** and the enol ether acetate **5***b* in *p*-dioxane and 20% HCl (1:1 v/v) gave the aldehyde **1***a* as the major product. These results are not entirely surprising since dioxane **12** might be expected to undergo cleavage and rearrangement to the aldehyde on heating with a mineral acid and, in the case of **5***b* cleavage at the ether oxygen would be expected

[5]The nature of the products from this reaction seems to clearly indicate that the normal oxonium ion resonance contribution of enol ethers, $R_2\overset{\ominus}{C}CH=\overset{\oplus}{O}—R'$, is of little importance in **5***b*. Rearrangement of **5***b* can be considered analogous to the thermal rearrangements of enolic ethers in general and allyl aryl ethers (Claisen rearrangement) producing in the case of **5***b* somewhat unexpected products because of the anomalous electronic distribution. Such thermally influenced rearrangements of this type for the most part are known (10) to proceed via first-order kinetics as depicted for **5***b* although it was not ascertained.



SCHEME 2

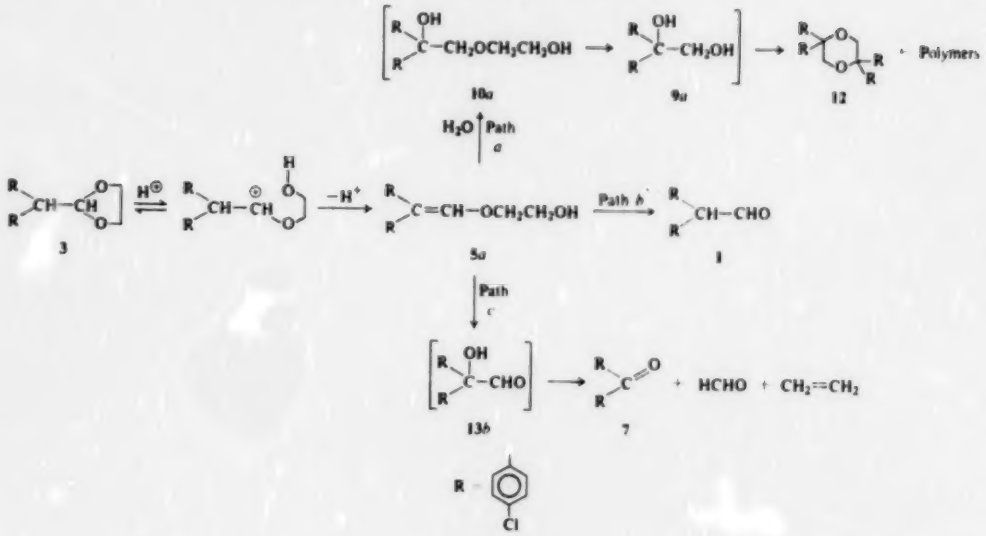
to occur more rapidly than hydrolysis of the acetate group such that an appreciable amount of the suspected "real" intermediate, the enol ether alcohol (**5***a*) is never available for rearrangement leading to dichlorobenzophenone **7**. In considering the transition state for rearranging **5***b* to **7**, the comparatively large acetate group in the vicinity of the reacting center restricts the number of configurations which may be assumed by the atoms involved, resulting in further reduction in entropy which is rate-retarding. Therefore, one would expect the enol ether alcohol (**5***a*) to rearrange as shown in Scheme 2 with a more positive entropy which would be comparatively rate-enhancing. The fact that the enol ether alcohol could not be isolated is consistent with this argument.

Variations[6] in the hydrolysis conditions of acetal **3***a* gave qualitatively but not quantitatively the same products, acetaldehyde **1***a* and dichlorobenzophenone **7**. Hydrolysis in 95% ethanol with 20% aqueous sulfuric acid (2:1 v/v) produced approximately equal quantities of **7** and **1***a*. Hydrolysis in 95% ethanol or 1,4-dioxane with concentrated sulfuric (10:1 v/v) afforded aldehyde **1***a* in good yields. Totally aqueous acidic conditions gave either no reaction or the dichlorobenzophenone **7** as the major product. These results imply that more aqueous conditions and hence more heterogeneous conditions favor production of **7**. Under more heterogeneous conditions solvolysis reactions would be minimized and intramolecular vapor phase reactions, which would be thermally influenced, become more important. This is consistent with a cyclic decomposition of **5***b* to **7** as delineated in Scheme 2. The intermediates formed in the hydrolysis of acetal **3***a* which are most tenable with our results are given in Scheme 3.

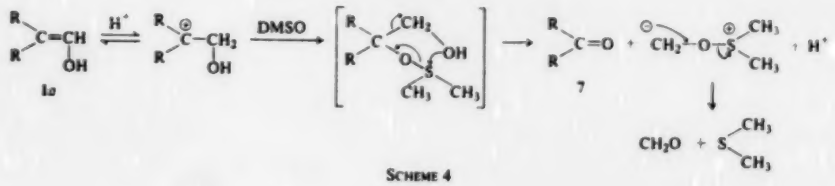
Preequilibrium protonation of **3** followed by decomposition to a resonance-stabilized carbonium ion would be expected (11). The enol ether alcohol (**5***a*) could be formed by deprotonation of this carbonium ion, and once formed, can undergo several reactions (paths *a*–*c*). Normal hydrolysis as in path *b* would lead to aldehyde **7**. Protonation of the enol ether oxygen followed by hydration of the double bond (path *a*) would lead to diethylene glycol **10***a* which in turn could decompose to ethylene glycol **9***a* ultimately leading to dimers and polymers. Protonation of the ether oxygen followed by intramolecular attack on the double bond and rearrangement would lead to the α-hydroxy aldehyde **13***b* which would decompose[7] to the dichlorobenzophenone **7**.

[6] Several classical methods for preparing aldehydes (Rosenmund and metal hydride reductions of the acid chloride, chromium oxide oxidation of the alcohol, etc.) were unsuccessful for **1***a*; in most cases the major isolable product was the dichlorobenzophenone **7**. The mechanistic implications of these results are not completely understood.

[7] The expected by-products of these disproportionation reactions are formaldehyde and ethylene. One would expect formaldehyde to polymerize under the reaction conditions, and attempts to trap it with various carbonyl derivatizing agents were unsuccessful. Likewise, ethylene could not be trapped as its dibromide; however, an n.m.r. hydrolysis study of **3***a* with aqueous D_2SO_4 in d_6-dimethylsulfoxide, which indicated the presence of **7** as well as trace amounts of **1***a*, showed a singlet of weak intensity at a chemical shift (τ 4.55) identical to that of authentic ethylene.



SCHEME 3



SCHEME 4

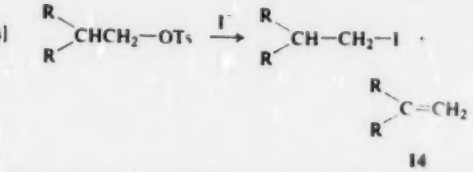
Our investigations were extended to include the *o,p'*-dioxolane **3***b* since commercial preparations of DDT contain the *o,p'*-isomer as a major component whose metabolism is qualitatively similar although quantitatively different (12). Dioxolanes **3***a* and *b* are electronically analogous and would be expected to undergo similar reactions. Under the hydrolysis conditions of **3***a* that afford only minor amounts of the expected aldehyde **1***a*, **3***b* affords quantitative yields of aldehyde **1***b*.

The anomalous hydrolysis of **3***a* seems to be manifested in the facility by which the benzhydryl carbon of this system can undergo oxidation. This reflects greater charge stabilization associated with the bis(*p*-chlorophenyl) system than with the *o,p'*-system which must be explained on the basis of steric arguments. CPK-Models[8] indicate that there are two sterically derived factors which would hinder or prevent oxidation of the benzhydryl carbon in the *o,p'*-system (**3***b*). There is steric hindrance to removal of the benzhydryl proton imposed by the *o*-chlorine,[9] and there is steric inhibition of resonance which would impair charge stabilization once the proton has been removed. Aldehyde **1***b* would be the expected hydrolysis product of **3***b* regardless of which of the two steric effects is more important in determining the course of the reaction.

Previous investigators (6) observed steric dependence in attempting to prepare the isomeric iodides from the corresponding tosylates of the

[8]Corey–Pauling–Koltun atomic models.

[9]A measure of this effect is evident from a comparison of the chemical shift of the benzhydryl proton in *p,p'*-DDT (τ 5.00) with that in *o,p'*-DDT (τ 4.25) and *o,p'*-DDD (τ 4.28); an ortho chlorine within the aromatic ring deshields the benzhydryl proton more than a para-substituted chlorine. See Keith *et al.* (13) for a discussion of the n.m.r. spectra of DDT-related compounds.

[4] 

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dichlorodiphenylethanols (eq. 4). The elimination product **14** was the sole product in the case of *p,p'*-isomer whereas the *o,p'*-isomer gave a mixture of the two products. On the other hand, the *o,o'*-isomer gave the iodide as the sole product. Steric factors are known (14) to play an important role in bimolecular elimination reactions. Steric hindrance to resonance stabilization of the product might also influence the reaction course in this case.

A steric dependence of this system was further demonstrated in our laboratory by observing the n.m.r. spectra of the aldehydes in dimethylsulfoxide (d_6-DMSO). In DMSO, **1***a*, is converted to its enol form almost quantitatively upon solution as evidenced by a decrease in the n.m.r. proton signal of the benzhydryl carbon. In most instances this enolization was accompanied by a small (< 10%) conversion to the dichlorobenzophenone **7**. Crystalline material isolated from the DMSO solutions had properties identical to those of authentic **7**. The *o,p'*-isomer undergoes a slower rate of enolization as measured by n.m.r.; however, there was no evidence to indicate reactions with DMSO. It was shown using the *o,p'*-isomer that the enolization rate in DMSO could be catalyzed by the addition of either acid or base. Shaking the protio-aldehyde in chloroform-*d* with D_2O in the presence of sodium carbonate resulted in the exchange of the benzhydryl proton for deuterium while the aldehyde proton remained unchanged. The *o,o'*-isomer[10] **1***c*, however, failed to undergo enolization in DMSO at temperatures ranging from 26 to 75 °C. In comparison, diphenylacetaldehyde enolizes in DMSO to a lesser extent than did the bis(*p*-chlorophenyl)acetaldehyde. From this result one infers that the electronic effects of the chlorine substituents as well as steric factors play a role in the enolization processes. In the case of the *p,p'*-isomer, the electronic effects must also influence subsequent reactions since the dichlorobenzophenone **7** was detected in its DMSO solutions. Since enolization of **1***a* appears to be very rapid in DMSO, it is probable that formation of **7** involves the enol. Steric hindrance to removal of the benzhydryl proton would be manifested if enolization were required to form a reactive species. Although there is no compelling evidence, the following pathway is proposed (Scheme 4).[11] Preequilibrium protonation of the enol could generate the bis(*p*-chlorophenyl) carbonium ion system which is susceptible to attack by oxygen of DMSO. The resulting labile alkoxysulfonium salt could undergo intramolecular attack at sulfur to afford **7**.

This work has shown that the bis(*p*-chlorophenyl) system in conjunction with a vicinal electron deficient carbon, such as is contained in the aldehyde moiety and possibly in a trichloromethyl group,[12] can undergo rather facile reactions involving the benzhydryl carbon usually resulting in an overall oxidation at this position which may be concomitant with the loss of the adjacent group. In comparing the oxidative propensities of the *p,p'*- and *o,p'*-systems, it is evident that the requisite removal of the benzhydryl proton is subject to the stereoelectronic requirements imposed by the chlorophenyl groups. The *o*-chlorophenyl compounds have much less tendency toward oxidation and double bond formation at their benzhydryl carbons. In light of this work, the possible intermediacy of the α-hydroxy aldehyde **13***b* in the formation of dichlorobenzophenone **7** during DDT metabolism is plausible. The ease of enolization of the *p,p'*-aldehyde **1***a* could facilitate its interactions in biological systems subsequently leading to redox products such as α-hydroxy aldehyde **13***b*. Our results also lend some credence to the corollary that, if such an aldehyde were formed *in vivo*, conjugates[13] involving the hydroxy group could activate the

[10]The aldehyde **1***c*, which was obtained from Aldrich Chemical Co., Milwaukee, Wisc., exhibited no unusual reaction properties.

[11]The use of polarizing agents to promote DMSO oxidations of alcohols has been reported (15) to produce alkoxysulfonium salts which undergo base-catalyzed decomposition to carbonyl compounds. The hydroxymethylalkoxysulfonium ion which could be formed from **1***a* may constitute a special case of this in which the hydroxymethyl group acts as an internal base to effect the stepwise decomposition to two carbonyl compounds.

[12]The compound 1,1-bis(*p*-chlorophenyl)-2,2,2-trichloroethanol has been shown (16) to pyrolyze to **7** and chloroform.

[13]Previous workers (17) have shown that DDT metabolite conjugates are formed, although their exact nature is not known. However, they do not appear to be conjugated with glucuronic or sulfuric acids.

molecule as an alkylating agent.[14] Nevertheless, the occurrence of such an aldehyde would implicate a host of new and interesting metabolites which will be described elsewhere. Although, it is not surprising that the aldehyde **1***a* has not been detected in DDT metabolism, earlier work (18) has shown that 2,2-bis(*p*-chlorophenyl)-ethanol (DDOH), a known DDT metabolite (1), is a substrate of crystalline liver alcohol dehydrogenase which oxidizes DDOH to **1***a*.

Experimental

Melting points were taken on a Fisher–Johns melting point apparatus and are corrected. The i.r. spectra were obtained with Perkin–Elmer 337 and 521 spectrophotometers. The n.m.r. studies were made with a Varian T-60 and an HA-100 spectrometer equipped with a variable temperature probe using tetramethylsilane (TMS) or sodium 2,2-dimethyl-2-silapentane-5-sulfonate (DSS) as internal references. Routine gas chromatograms were obtained with a Varian Aerograph model 1868-40 chromatograph equipped with a tritium detector. The low-resolution mass spectra were obtained with an LKB 9000 gas chromatograph-mass spectrometer. Thin-layer chromatograms were run on Uniplate, Silica Gel GF plates 250 and 500 μ in thickness and were developed in methylene chloride. The bands were detected with u.v. light.

Formation of 2,2-Bis(p-chlorophenyl)acetaldehyde (1a)

(a) From Darzens Condensation

To a solution of 7.5 ml (0.077 mol) of ethyl chloroacetate and 10 g (0.04 mol) of 4,4′-dichlorobenzophenone (Eastman Organic Chemicals) in 25 ml of anhydrous benzene under nitrogen was added 6.0 g (0.12 mol) of sodium hydride (50% dispersion) with stirring over a 2 h period. The reaction mixture was stirred for 16 h at room temperature and poured into 50 ml of ice-cold 25% HCl solution. The resulting suspension was extracted with two 50-ml portions of benzene. The combined extracts were dried over anhydrous sodium sulfate and evaporated to dryness. The partially solidified residue was recrystallized from methanol, affording 9.5 g of ethyl β,β-bis(*p*-chlorophenyl)glycidate melting at 98–105°. Without further purification this material was dissolved in 40 ml of ethanol and the resulting solution was refluxed for 6 h with 15 ml of 35% aqueous potassium hydroxide solution. The ethanol was removed by rotary evaporation and the remaining mixture was diluted with 25 ml of distilled water and extracted with two 30-ml portions of ether. The aqueous phase was acidified (p*H* 4–5) with 20% hydrochloric acid, forming a milky solid suspension. The suspension was extracted with two 50-ml portions of ether and the combined extracts were washed with distilled water, dried over anhydrous sodium sulfate, and evaporated to an oily residue. Decarboxylation of the crude material was accomplished by heating in an oil bath at 140–160° under reduced pressure (water aspiration) for 30 min. The crude product **1***a* weighed 4.5 g (60%). The aldehyde was purified by dissolving in 10 ml of methanol and adding the resulting solution dropwise with stirring to 25 ml of saturated sodium bisulfite solution. The mixture was stirred at room temperature for 5 h and the solid suspension was removed by filtration. The cake was washed with water, 2-propanol, and then ether before drying under vacuum. The aldehyde was regenerated prior to use by heating portions of the bisulfite addition product with 10% sodium carbonate solution at 75° until an oil separated (15–30 min). The pure aldehyde was obtained by extraction into ether and had the following spectral properties: i.r., λ (neat) 5.80 (C=O), 3.49 (CH), 13.2 (C—Cl); n.m.r., τ (chloroform-*d*) 0.10 (doublet, J = 2.4 Hz, 1H, CHO), 3.00 (multiplet, 8H, aromatics), 5.08 (doublet, J = 2.4 Hz, 1H, benzhydryl).

The *p*-nitrophenylhydrazine derivative prepared according to the method of Shine (19) contained one molecule of methanol of crystallization and melted at 85–88°. When this material was recrystallized from ether – petroleum ether, the methanol was removed to give a crystalline compound melting at 135–138 °C: i.r., λ (Nujol) 3.03 (NH), 6.26 (C=N), 7.58, 7.72 (NO_2); n.m.r., τ (dimethylsulfoxide-d_6) 1.84, 2.95 (pair of doublets, J = 9 Hz, for *p*-nitrophenyl aromatics); 2.10, 4.82 (pair of doublets, J = 6 Hz, for azomethinyl and benzhydryl protons); 2.57 (multiplet for bis(*p*-chlorophenyl) aromatics).

The *p*-nitrophenyl hydrazone of the dichlorobenzophenone **7** was prepared according to the same procedure and melted at 213–215°: i.r., λ (Nujol) 3.02 (NH), 6.30 (C=N), 7.55, 7.90 (NO_2); n.m.r., τ (dimethylsulfoxide-d_6) 1.97 (doublet, J = 9 Hz, 2H of *p*-nitrophenyl aromatics); 2.64 (multiplet, 2H of *p*-nitrophenyl aromatics, 8H of bis(*p*-chlorophenyl) aromatics).

(b) From Hydrolysis of 2-(4,4′-Dichlorobenzhydryl)-1,3-dioxolane (3a)

To a solution of 85 mg (0.28 mmol) of dioxolane in 5 ml of 95% aqueous 1,4-dioxane was added 0.4 ml of concentrated H_2SO_4. The resulting solution was magnetically stirred and refluxed for 3 h. The 1,4-dioxane was removed by rotary evaporation and the aqueous phase doubled in volume with distilled water to 3 ml. The aqueous solution was then extracted with two 3-ml portions of anhydrous ether and the combined extracts were dried over anhydrous Na_2SO_4 containing solid Na_2CO_3. Evaporation of the ether extracts under a nitrogen stream followed by pumping *in vacuo* gave 79 mg of a mixture composed of the 2,2-bis(*p*-chlorophenyl) acetaldehyde **1***a* and starting material. The aldehyde which was purified by preparative t.l.c. (40 mg, 55% yield) was identical in every respect to aldehyde obtained via the Darzens synthesis. Longer reflux times (6–8 h) gave increasingly higher yields of aldehyde under these conditions.

Solvolysis of 2-(4,4′-Dichlorobenzhydryl)-1,3-dioxolane (3a) in Acetic Acid

To a solution of 8 ml of glacial acetic acid and 0.05 ml of concentrated H_2SO_4 was added 155 mg (0.5 mmol) of

[14]The formation of the symmetrical dioxane **12** previously discussed can be considered a head-to-tail alkylation of two molecules of the acetoxyethanol **9***b* via displacement of the acetate groups. This reaction appears to be facile since it occurs directly on a silica gel t.l.c. plate during development. This compound was also found as a reaction product of unsuccessful attempts to form amino acid Schiff bases of aldehyde **1***a*.

dioxolane **3a**. The resulting solution was heated at 100 °C for 1 h. The acetic acid was removed by lyophilization and the residue pumped *in vacuo* over P_2O_5. The residual oil was dissolved in chloroform-*d* and examined by n.m.r. spectroscopy. The spectrum indicated a mixture of products of which the three major components were tentatively identified as 2,2-bis (*p*-chlorophenyl)acetaldehyde (**1a**), 4,4′-dichlorobenzophenone (**7**), and 1,1-bis(*p*-chlorophenyl)-1-acetoxyethanol (**9b**) in an approximate ratio of 3:1:3. Preparative t.l.c. of the mixture gave 45 mg of aldehyde **1a** and 15 mg of dichlorobenzophenone **7** along with 27 mg of dimer **12** and 20 mg of polymeric material (dark brown material remaining at the origin) both of the latter materials being decomposition products of the acetoxyethanol **9b**. A small amount (10 mg) of pure dimer **12** was obtained by repeated preparative t.l.c. and had the following properties: i.r., λ ($CHCl_3$ film) (aromatic) 6.70, 12.2; (C—O—C) 8.88, 9.18, 9.85; n.m.r., τ (chloroform-*d*) 2.99 (multiplet, aromatics), 4.65, 5.89 (doublets, J = 2.0, Hz, methylene protons); τ (benzene-d_6) 3.10 (multiplet, aromatics), 5.19, 6.17 (doublets, J = 2.0, Hz, methylene protons).

Anal. Calcd. for $C_{28}H_{20}O_2Cl_4$: C, 63.42; H, 3.77. Found: C, 63.19, H, 4.38.

1,1-Bis(p-chlorophenyl)-3-oxa-1-pentenyl-5-acetate (Enol Ether Acetate (5b))

To a solution of 20 ml of acetic anhydride and 2 ml of concentrated H_2SO_4 was added 2.0 g (65 mmol) of the dioxolane **3a**. The resulting solution was heated at 100 °C with stirring for 0.5 h. On cooling, the reaction mixture was poured into ice water (approximately 30 ml) and extracted with two 50-ml portions of anhydrous ether. The combined extracts were washed with saturated Na_2CO_3 solution, water, and then dried over anhydrous Na_2SO_4 followed by evaporation. The residue remaining (approximately 3.2 g) was chromatographed on a column of Silcar CC-7 (40 g) using a mixture of hexane:chloroform:methanol (3:2:1) as the eluting solvent. The fractions were analyzed with t.l.c. and combined accordingly. The residue remaining on evaporation of the solvent weighed 1.87 g (91%). A portion of this material was crystallized twice from *n*-hexane affording a crystalline hygroscopic solid melting at 73–75 °C: i.r., λ (neat) (C=O) 5.75, (O—C=C) 6.20; n.m.r., τ (chloroform-*d*) 2.76 (multiplet, aromatics); 3.54 (singlet, enolic proton); 5.80 (multiplet, methylene protons); 7.97 (singlet, acetate CH_3).

Anal. Calcd. for $C_{18}H_{16}O_3Cl_2$: C, 61.56; H, 4.56; O, 13.77; Cl, 20.22. Found: C, 61.22; H, 4.74; O, 13.58; Cl, 20.04.

Formation of 4,4′-Dichlorobenzophenone (7)

(a) From Hydrolysis of 2-(4,4′-Dichlorobenzhydryl)-1,3-dioxolane (3a)

To a mixture of 10 ml of 1,4-dioxane and 10 ml of 20% aqueous HCl was added 1.0 g (3.2 mmol) of dioxolane **3a**, and the resulting mixture was refluxed for 3.5 h. The solution after cooling to room temperature was diluted with additional water to 50 ml and extracted with two 30-ml portions of anhydrous ether. Combined ethers were washed with water, dried over anhydrous Na_2SO_4, and then evaporated. The residue was dissolved in 10 ml of methanol and gave on prolonged cooling 0.21 g (30%) crystalline material identical in every respect to authentic 4,4′-dichlorobenzophenone **7**. The mother liquor was evaporated and examined by n.m.r. spectroscopy. The remaining material (0.52 g) consisted of a mixture of dioxolane **3a**, dichlorobenzophenone **7**, and aldehyde **1a** (1:1:2). The total yield of **7** was approximately 57%.

(b) From Solvolysis of Enol Ether Acetate (5b)

A solution of 3 ml of glacial acetic acid and 0.1 ml of concentrated H_2SO_4 containing 83 mg (0.24 mmol) of enol ether acetate was heated at 100 °C for 1 h. The acetic acid was removed by lyophilization and pumping *in vacuo* over P_2O_5. The residual oil was examined by n.m.r. spectroscopy and consisted primarily of 4,4′-dichlorobenzophenone (**7**) and 1,1-bis(*p*-chlorophenyl)-1-acetoxyethanol (**9b**). The oil was transferred to preparative t.l.c. plates by streaking, and the plates were developed in methylene chloride. Three major bands were detected and the middle band was removed (24 mg, 40%) and found to be identical in every respect to 4,4′-dichlorobenzophenone (**7**). The other two bands were indicative of the dimer and polymeric decomposition products of the acetoxyethanol **9b** and were not isolated; a band was found at the origin and one near solvent front which had light blue fluorescence under short wave u.v. light.

2-(o,p′-Dichlorobenzhydryl)-1,3-dioxolane (3b)

To a solution of 6.9 g (0.028 mol) of 1-(*o*-chlorophenyl)-1-(*p*-chlorophenyl)-2,2-dichloroethane in 25 ml of ethylene glycol was added 7.05 g (0.051 mol) of powdered anhydrous potassium carbonate. The mixture was refluxed at 190–200° for 16 h and poured into ice water. The aqueous suspension was extracted with two 25-ml portions of ether, and the combined extracts were dried over anhydrous sodium sulfate and taken to dryness. The crude residue (6.2 g) afforded 4.0 g (59%) of crystalline material melting at 73–76° when crystallized from methanol: n.m.r., τ (chloroform-*d*) 2.80 (8H multiplet for aromatics); 4.54, 5.30 (2H pair of doublets, J = 4 Hz, benzhydryl proton and methinyl proton of dioxolane ring); 6.26 (4H multiplet, dioxolane ring).

2-(o-Chlorophenyl)-2-(p-chlorophenyl)acetaldehyde (1b)

A solution of 9.4 g (0.034 mol) of **3b** in 25 ml of *p*-dioxane and 50 ml of 25% aqueous sulfuric acid was refluxed with stirring for 5 h. The reaction mixture on cooling was extracted with two 50-ml portions of ether. The combined ether extracts were extracted twice with dilute sodium bicarbonate solution and washed twice with distilled water. The ether phase was dried over anhydrous sodium sulfate and evaporated to a liquid residue weighing 9.2 g. The liquid was purified by formation of the bisulfite addition product as described for **1a** except the stirring time was increased to 24 h. A 7.0 g portion of the addition product when decomposed with dilute sodium carbonate solution gave 5.0 g (81%) of pure aldehyde **1b** with the following spectral properties: i.r., λ (neat) 5.75 (C=O), 6.65 (aromatic), 13.3 (C—Cl); n.m.r., τ (chloroform-*d*) 0.16 (singlet, 1H, CHO), 2.80 (multiplet, 8H, aromatics), 4.67 (singlet, 1H, benzhydryl).

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